REMARKS

In accordance with the above amendments, claims 115 and 127 have been amended. Thus, claims 115, 116, 118, 120-121 and 126-131 presently remain under consideration.

The withdrawal of the previous objections to the specification and claims, together with the previous rejections under 35 USC §§ 102(b) and 103(a) in view of applicants' previous amendments, are gratefully acknowledged.

Several new grounds of rejection have been raised by the Examiner with respect to the application and these will next be addressed.

Rejections Under 35 USC § 112

Written Description

Claims 127 and 128 have been rejected under 35 USC § 112, first paragraph, as failing to comply with the written description requirement. Thus, the phrase "during or after activation of said T cells" in claim 127 has been replaced by a reference to "prior to fixation or during the activation of said T cells". This language, as indicated by the Examiner, does find support in the specification, for example, at page 13, lines 17-19, and in originally filed claim 68. In view of the amendment to claim 127, the Examiner is respectfully requested to reconsider and withdraw the rejection of claim 127 stated above and, inasmuch as claim 128

depends from claim 127, the rejection should also be withdrawn with respect to that claim.

Use of Abbreviations "T_{ck}" and "T_{tcr}"

Claims 115, 116, 118, 120, 121 and 126-131 have also been rejected under 35 USC § 112, second paragraph, as being indefinite and ambiguous in the recitation of the abbreviation "T_{ck} cells and T_{tcr} cells". In this regard, the first mention of T_{ck} cells in claim 115 has been amended to define these as being "cytokine stimulated T cells". Similarly, the first reference to T_{tcr} cells in claim 127 now defines these as being "T cell receptor-stimulated T cells". It is believed that these clarifying amendments overcome the subject rejection and reconsideration and withdrawal of this rejection is respectfully requested.

Definitions

A. The claims 115, 116, 118, 120, 121 and 126-131 have also been rejected under 35 USC § 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps and, in particular, with regard to the use of the term "selectively inhibit" the ability of T_{ck} cells to induce proinflammatory... for failing to include a step with a test compound as applied to something other than T_{ck} cells to screen out those test compounds which fail to selectively inhibit T_{ck} cells.

In response to this rejection, claim 115 has been amended to clarify what is meant by "selectively inhibit". Claim 115 now makes it clear that selective inhibition is based on a comparison between the effects using T_{ck} cells and the effects using another T cell population. This is based on the general definition of "selectively inhibits" at page 5, lines 21-23. This passage defines "selectively inhibits" by comparison with "other T cell populations, such as T cell populations. Claim 127 gives a more specific comparison with T_{tcr} cells.

B. Claim 115 and dependent claims thereof have been rejected under 35 USC § 112, second paragraph, as being incomplete and also for omitting essential steps with respect to omitting a step which enables the skilled artisan to distinguish monocyte produced cytokines from T_{ck} cells produced. In this regard, claim 115 has been amended as suggested by the Examiner to state that T_{ck} cells are fixed prior to the co-culturing with monocytes. In view of this amendment, the Examiner is respectfully requested to reconsider his position and withdraw this rejection.

C. Claim 127 and dependent claims thereof have been rejected under 35 USC § 112, second paragraph, as being indefinite by the recitation of the term "to a greater extent". A clarifying amendment has been made to claim 127 so that the claim now refers to the ability to selectively inhibit the T_{ck} related response when

compared to the inhibition of the T_{tcr} related response. The meaning of this language should now be clear as it involves a direct comparison between the two experimental groups.

Rejection of Claims Under 35 USC § 103

Claims 115, 116, 118, 120, 121, 126 and 129-131 have been rejected under 35 USC § 103(a) as being unpatentable over Sebbag et al (Eur. J. Immunol. 1197 Mar;27(3):624-32) in view of McInnes et al (Immunol. Today. 1998 Feb;19(2):75-79). This rejection is respectfully traversed.

The Examiner has rejected the claims as being unpatentable over Sebbag et al in view of McInnes et al. The Examiner has discussed in particular a number of passages in the Sebbag et al paper. Sebbag et al, as a whole, describes an *in vitro* model using artificially stimulated T cells. Sebbag et al includes some unsupported speculation that the results presented using this model may be of relevance in some *in vivo* situations. However, there is no evidence in Sebbag et al that the cells or interactions described in that *in vitro* model have any relevance *in vivo*.

In contrast, the present application demonstrates for the first time that T_{ck} cells actually have the same effect or function as activated T cells that are present in chronic inflammatory disease such as T cells from rheumatoid synovial tissue.

Without the knowledge that these cells are actually equivalent in terms of effect or function to the activated T cells found in chronic inflammatory tissue, the skilled person would have had no reason to expect that an assay method as claimed would have had any utility in identifying potential therapeutic agents. The effects of a compound on a cell line that has been artificially generated *in vitro*, which is used in an artificial *in vitro* cell contact model, cannot be assumed to have any relevance in relation to the possible effects of the same compound *in vivo*.

The various models described by Sebbag et al are based on artificially generated situations. For example, in some embodiments the T cells were stimulated with single cytokines, while in other experiments they were stimulated with specific combinations of two cytokines. There would have been no particular reason to believe that T cells that were produced in isolation *in vitro* by such specific cytokine stimulation would have any similarity in function or capability to those activated T cells present *in vivo*.

Sebbag et al unsurprisingly includes some broad speculation as to the relevance of the results that it reports, but none of this speculation is supported by any data and the skilled reader of Sebbag would understand that the methods described are based on a simple *in vitro* model. There would be no reason to believe that

such a model would have any relevance when considering screening for drugs suitable for use *in vivo*. Sebbag et al suggests that the data generated using their model supports a variety of theories. However, this does not mean that the interactions and effects seen using their model will have direct relevance *in vivo*.

In contrast, the present application provides data showing that T_{ck} cells have the same effect or function as T cells isolated from RA synovia. Because both of these T cell groups have the same signaling pathways and effect or functions, it is reasonable to assume that they will both also respond to the same ligands or counter-ligands. On the basis of the data presented in the present application, it can therefore be assumed that methods as now claimed will be of use in identifying compound *in vitro* that may be of clinical use *in vivo*. The usefulness of such methods would not have been predicted based only on the information provided by Sebbag et al. Sebbag et al merely allows specific information to be obtained relating to the effects of an artificially generated cell line on monocytes *in vitro*. Any effect of additional compounds that were used to treat the T cells in the Sebbag et al method would not be linked to any potential clinical effect. There would be no particular reason to believe that effects on such artificially generated cells in an *in vitro* model would be predictive of effects to be achieved *in vivo*.

With hindsight, it may be possible to see how the methods of Sebbag et al could have been modified in order to reach the present invention. However, it is submitted that such modifications would not have been made based only on the information provided by Sebbag et al. It was not until the additional information provided in the present application relating to the similarities in effect or function between the different T cell types became available that the utility of such an *in vitro* model will have become apparent.

It would clearly have been possible for the methods of the present invention to have been carried out using different types of T cells. Such methods could be used to try to identify agents that would inhibit the effects of such T cells on cytokine production by monocytes. However, the skilled person would have had no way of predicting whether those compounds would have any effect *in vivo* or whether they might be useful in the treatment of any particular diseases. The skilled person would have had no reasonable expectation that the compounds identified in such an assay would be effective. By demonstrating the functional equivalence of T_{ck} cells with the activated T cells present in chronically inflamed tissue, the inventors have opened up a new way of identifying potential therapeutic compounds that could be used in the treatment of chronic inflammation.

The Examiner has combined Sebbag et al with McInnes et al in the present rejection. However, McInnes et al, it is submitted, would provide the skilled reader of Sebbag et al with no further clues as to the usefulness of artificially generated T cells in screening for potential therapeutic compounds. McInnes et al simply discusses possible targets for therapy in rheumatoid arthritis. There is nothing there to suggest that the particular T cells that are artificially generated in Sebbag et al would actually show the same effect or function as the *in vivo* T cells in rheumatoid arthritis.

The skilled reader of Sebbag and McInnes could have utilized the model described by Sebbag et al to identify compounds capable of interfering with the T cell - monocyte interaction. However, it is not clear why they would have done so. There is no particular reason to believe that compounds identified in this way would have had any effect on similar processes occurring *in vivo*.

In view of the above, it is believed that this rejection should not stand and reconsideration and withdrawal of this rejection is respectfully requested.

Claims 127 and 128 have also been rejected under 35 USC § 103(a) as being unpatentable over the above combination as applied to claims 115, 116, 118, 120, 121, 126 and 129-131 and further in

view of Parry et al (J. Immunol. 1997 Apr 15;158(8):3673-3681). This rejection is also respectfully traversed.

As submitted previously, Parry et al describes the formation of T_{tcr} cells. However, there is no indication here that these cells may have any particular relevance to the situation *in vivo*, or that any comparison between such cells and the T_{ck} cells described in Sebbag et al may be of clinical relevance.

Clearly, there are many artificial means that could be used to activate T cells *in vitro*. However, the important question is whether any of these will effectively mimic those T cells which are activated *in vivo*. For example, T_{tcr} cells are an example of a type of activated T cells that can be artificially produced (as described by Parry et al). However, based on the teaching of Parry et al, the skilled reader would not know whether those cells would actually be useful in a screening assay for potentially therapeutic compounds.

The Examiner has referred to passages in Parry et al which suggest that the T_{tcr} cells induce monocyte IL-10 production. The Examiner also cites some general comments from Parry et al relating to trials that have been carried out *in vivo* using IL-10. The Examiner concludes from this that it would have been obvious to select a compound that inhibits T_{ck} cells in favor of T_{tcr} cells. However, this reasoning is believed to be available only based on

hindsight. The comparative effects of these two artificially generated cell lines *in vitro* can only be assumed to be of clinical relevance once it has been determined that the functions of such cells mimic functions that are occurring *in vivo*. The fact that T_{tcr} cells can induce monocyte IL-10 secretion *in vitro* does not mean that compounds identified using such cells would also be effective on any T cells present *in vivo* in an inflammatory disease, or that such compounds would be effective in inducing IL-10 secretion *in vivo*. There is no evidence at all to support such a conclusion in any of the documents cited by the Examiner. Similarly, as explained above, there is no evidence at all in the prior art that results obtained using T_{ck} cells would have had any utility in predicting the effects of compound *in vivo*.

In view of the above amendments, taken together with the remarks herein, the Examiner is respectfully requested to reconsider the rejections and objections, withdraw the rejections and objections contained in the present Office Action and allow the claims.

Should minor issues remain which, in the opinion of the Examiner, could be resolved by telephone interview, he is invited

to contact the undersigned attorney at his convenience to discuss same in an effort to resolve any remaining issues and expedite prosecution of this application.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the foregoing Amendment to a final Official Action dated July 19, 2007, a Petition for Extension of Time Under 37 CFR 1.136(a) for one month and a Transmittal Letter in connection with application Serial No. 10/088,801 of inventor(s), Fionula M. Brennan et al., filed September 18, 2002, for "THERAPEUTIC METHODS AND COMPOUNDS" are being sent by facsimile transmission to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on October 18, 2007.

April C. Nelson
On Behalf of C. G. Mersereau

Date of Signature: October 18, 2007